An update from the SU2C ovarian cancer dream team

Alan D’Andrea, M.D.
The Fuller-American Cancer Society Professor
Co-Leader, SU2C Dream Team on Ovarian Cancer
Director, Susan F. Smith Center for Women’s Cancer
Dana-Farber Cancer Institute
Harvard Medical School
Boston MA.
DNA Repair Therapies for Ovarian Cancer

Alan D’Andrea, MD
Dana-Farber Cancer Institute
Elizabeth Swisher, MD
University of Washington School of Medicine
OVARIAN CANCER DREAM TEAM
DNA Repair Dream Team
Impacting Ovarian Cancer Mortality Through Novel Therapies and Prevention

Advocacy
Crase • Polinsky • Gavin

Therapy
CDKi + PARPi
PI3Ki + PARPi
ATRi + PARPi

Prevention
MAGENTA
WISP

TEAM SCIENCE
University of Washington • Dana Farber Cancer Institute • Mayo Clinic • University of Chicago • MD Anderson • Memorial Sloan-Kettering
Elizabeth Swisher • Alan D'Andrea • Scott Kaufmann • Gini Fleming • Karen Lu • Maria Jasin
Aim 1: Basic Science

*Mechanisms of Sensitivity and Resistance to PARPi*

Aim 2: Clinical trials with novel therapies

*Novel Drug Combinations to Extend PARPi Use*

Aim 3: Clinical trials

*OC Risk Assessment and Prevention*
Aim 1
Mechanisms of Sensitivity and Resistance to PARPi

Rationale:
- 50% of Serous OC have DNA Repair (HR) Deficiency
- Olaparib approved for OC with BRCA1/2 mutations
- Need for identifying additional OC with PARPi sensitivity
- Need to identify mutations in other genes which cause OC
An enzyme involved in DNA repair
Binds directly to DNA damage
Recruits other proteins to the site of DNA repair
Ovarian Tumors are Hyperdependent on PARP

Poly (ADP-ribose) polymerase (PARP)

Modified from Alan Ashworth
BRCA2 is a Fanconi Anemia Gene

7691 insAT: + - + + - -
9900 insA: - + + - + +
Discovery of the Fanconi Anemia/BRCA DNA Repair Pathway
Discovery of the Fanconi Anemia/BRCA DNA Repair Pathway

Mutations in any of these 20 genes:
1) Identify Tumors which will respond to a PARPi
2) Identify Women at risk of developing OvCancer
Aim 1: Basic Science

*Mechanisms of Sensitivity and Resistance to PARPi*

Aim 2: Clinical trials with novel therapies

*Novel Drug Combinations to Extend PARPi Use*

Aim 3: Clinical trials

*OC Risk Assessment and Prevention*
Aim 2 objective: Extend PARP inhibitor efficacy to HR-proficient tumors

Agents that inhibit HR

HR-PROFICIENT + HR-DEFICIENT

PARP - Inhibitor

PARPi + CDKi – Aim 2A

PARPi + PI3Ki – Aim 2B

PARPi + ATRi – Aim 2C
Mouse Models demonstrate that a PARP inhibitor and a PI3K inhibitor are synergistic.


Wulf G, Liu J, Palakurthi S, Matulonis U
10 out of 27 patients with relapsed OC had partial responses to this drug combination.

* 3 patients were excluded due to missing lesion diameters at baseline and follow up.
New Clinical Trial Added to SU2C Portfolio: Niraparib + Pembrolizumab (NCT02657889)
(New Catalyst Program at SU2C)
Phase 1/2 Trial of Niraparib with Pembrolizumab in Recurrent Ovarian or TN-Breast Cancer

Start treatment 8 weeks 12 weeks Development of PD

Screening sign IC

Baseline Biopsy

On Treatment Biopsy

Biopsy upon Progression

P. Konstantinopoulos

PARPi + immune checkpoint blockade Catalyst project
Importance of Functional Tests in Predicting PARPi Resistance: Generation of Ovarian Cancer Organoid Cultures

1. Harvest tissue / obtain tissue biopsy
2. Dissociate tissue into functional units
3. Enrich for stem cells
4. Niche factors: R-spondin, WNT3A, Retinoic acid, GSK3β inhibitors, TGF-β inhibitors
5. Noggin, Activin A, Gastrin, p38 inhibitors
6. ECM factors: Collagen, Entactin, Fibronectin, Lamin
7. 7-10 days
Fresh Ovarian Tumor Cells on DAY 1
High Grade Serous Ovarian Tumor Organoids-Day 7

These organoids (microtumors) can be directly tested for their sensitivity to new drugs
Aim 1: Basic Science

Mechanisms of Sensitivity and Resistance to PARPi

Aim 2: Clinical trials with novel therapies

Novel Drug Combinations to Extend PARPi Use

Aim 3: Clinical trials

OC Risk Assessment and Prevention
Aim 3

OC Risk Assessment and Prevention

Rationale:
- 20% of OC caused by germline mutations in OC genes
- RRSO effective at decreasing OC mortality in high-risk women
- Genetic testing underutilized
- Not all women willing to undergo RRSO prior to menopause

(Walsh et al, PNAS, 2011)
Aim 3

OC Risk Assessment and Prevention

**Rationale:**
- 20% of OC caused by germline mutations in OC genes
- RRSO effective at decreasing OC mortality in high-risk women
- Genetic testing underutilized
- Not all women willing to undergo RRSO prior to menopause

Aim 3A
Defining OC Gene Risk

Aim 3B MAGENTA
Genetic Risk Assessment

Aim 3C WISP
Surgical Prevention

SU2C-OCRF-OCNA-NOCC Ovarian Cancer Dream Team Grant
Rationale:
- 20% of OC caused by germline mutations in OC genes
- RRSO effective at decreasing OC mortality in high-risk women
- Genetic testing underutilized
- Not all women willing to undergo RRSO prior to menopause
Aim 3A: Defining Ovarian Cancer Gene Risk

- Increased OC patients sequenced (2221 patients to date)
- No good publically available control population
- Sequenced 10,000 cancer free women from WHI for breast and ovarian cancer susceptibility genes
- Created Flossies database for public access
  - URL: https://whi.color.com/
BRCA1 and BRCA2

Important DNA Repair Genes

- 16% of ovarian cancer is caused by inherited mutations in BRCA1 and BRCA2
- BRCA1 mutations: 40% lifetime risk of OC
- BRCA2 mutations: 20% lifetime risk of OC
- 50–80% lifetime risk of breast cancer
- Olaparib is a PARP inhibitor approved for recurrent OC with BRCA1/2 mutations (after 3 previous lines of treatment)
1/5 of Inherited Mutations for OC Are in Genes Other than BRCA1 or BRCA2
1/5 of Inherited Mutations for OC Are in Genes Other than *BRCA1* or *BRCA2*

These are other Genes in the Fanconi Anemia/BRCA Pathway
A Family Gift

- All women with ovarian cancer should have genetic testing
Why should all women with ovarian cancer have Genetic Testing?

- Identifies cancer risk to other organs
- Allows other family members to know they are at risk
- 1/3 of inherited OC occurs in women with no family history of breast or ovarian cancer
- 40% of inherited OC occurs in women who are not younger than typical.
- Knowing your genetic status may be important for choosing therapy
Aim 3A: Defining OC Gene Risk
Aim 3B MAGENTA: Genetic Risk Assessment
Aim 3C WISP: Surgical Prevention
Assess how well we can deliver genetic testing for breast and ovarian cancer risk to women in their living room

**GOAL**

**TARGET Population:**
- Women without ovarian cancer
- Age ≥30
- No prior genetic testing

**Personal history BC or family history BC/OC**
(Group 1, N=2,250)

**Relative with known mutation**
Cascade testing
(Group 2, N=750)

SU2C-OCRFA--NOCC Ovarian Cancer Dream Team Grant
Complete the eligibility questionnaire to find out if you’re eligible

Complete baseline questionnaires

Read and electronically sign the online consent

Provide family history information and begin genetic testing process through Color Genomics¹

Pre-genetic testing education or counseling over the phone

Receive kit in the mail, provide saliva, and send back

Receive genetic test results

Post-genetic testing report or counseling over the phone²

Complete questionnaires after receiving your genetic test results

• 3 months
• 1 year
• 2 years

¹ Color Genomics owns and operates a CLIA licensed and CAP-accredited laboratory in California, U.S.A. that will be performing the genetic testing.

² All participants with a positive test result will receive genetic counseling over the phone.
Challenges

– Regulatory:
– Online Consent
  • 1ˢᵗ study at MD Anderson that uses online consent
  • Distress Plan
  • How can you provide support to someone who is distressed over the results they are receiving?
    – Setting up triggers through the questionnaires

– Legal:
– Ordering physician: Practicing medicine across state lines
– Genetic counseling: Licensing
  • Using genetic counselors from Color Genomics
The Tubal Hypothesis

A majority of serous ovarian and peritoneal carcinomas are actually seeded from cancer cells from the tubal epithelium.
**Inclusion Criteria:**
- Age 30–50
- Premenopausal
- Known mutation in OC gene

*Scripted counseling on recommended age for oophorectomy*

**Interval Salpingectomy**

**Delayed Oophorectomy**

**RRSO**

**PRIMARY Outcome:** Sexual Function (FSFI)

**SECONDARY Outcomes:**
- Vasomotor symptoms (MRS)
- Psychological symptoms (HADS)
- Pathological results (TIC, carcinoma)
Study Design

270 evaluable patients recruited into one of two arms

- Arm 1: interval salpingectomy with delayed oophorectomy (ISDO) with approximately 135 patients
- Arm 2: risk-reducing salpingo-oophorectomy (RRSO) with approximately 135 patients.

- Patient self-select arm, but MDs are mandated to recommend RRSO for BRCA1 carriers at age 40 and BRCA2 carriers at 45, if choose to delay BSO, then must reiterate that recommendation yearly.
RECOMMENDATIONS FOR HIGH-RISK WOMEN

Women at increased risk of ovarian cancer based on a genetic mutation are recommended to undergo removal of the fallopian tubes and ovaries (RRSO) by age 40 for BRCA1 and by age 45 for BRCA2.

For gene mutations including MLH1, MSH2, MSH6, PMS2, BRIP1, RAD51C, and RAD51D, there are recommendations to consider RRSO, although age is not specified.
GOAL OF TRIAL
To determine whether interval salpingectomy, followed by delayed oophorectomy (ISDO) can improve sexual functioning and menopausal symptoms compared to standard risk-reducing salpingo-oophorectomy (RRSO).

ELIGIBILITY
Pre-menopausal women between the ages of 30 and 50 with a documented mutation in one of the following eleven (11) ovarian cancer genes: BRCA1, BRCA2, BRIP1, PALB2, RAD51C, RAD51D, BARD1, MSH2, MSH6, MLH1, or PMS2.* (ie, genes in the Fanconi Anemia/BRCA Pathway)
CHOICE 1: RISK-REDUCING SALPINGO-OOPHORECTOMY
The removal of both ovaries and the fallopian tubes
• This is standard of care
• Most effective preventative measure: reduces the risk of ovarian cancer by 85-90%
• Can also reduce the risk of breast cancer
• If no personal history of breast cancer, can take hormone replacement therapy to reduce menopausal symptoms

• WHAT ARE THE DOWNSIDES?
• Causes menopause, symptoms of which include hot ashes, night sweats, vaginal dryness, mood changes and sleep disturbances
• Premature menopause may also increase the risk of other important health conditions, such as osteoporosis and cardiovascular disease
CHOICE 2: INTERVAL SALPINGECTOMY WITH DELAYED OOPHORECTOMY

The removal of the fallopian tubes, while temporarily delaying the removal of the ovaries
• Not yet proven to be effective at preventing ovarian cancer
• Retains ovaries, which helps delay the onset of menopause
• Avoiding premature menopause decreases the risk of some health conditions

WHAT ARE THE DOWNSIDES?

Research indicates that not all ovarian cancers originate in the fallopian tubes, so this surgery is not as effective in reducing risk as a salpingo-oophorectomy
May develop ovarian cancer
Requires a second surgery to remove the ovaries
Not likely to reduce the risk of breast cancer
SU2C-OCRF-OCNA-NOCC Ovarian Cancer Dream Team Grant

Mayo Clinic
Rochester, MN

UW Medicine
Seattle, WA

MD Anderson
Houston, TX

UC Medicine
Chicago, IL

Dana-Farber
Boston, MA

MSKCC
New York, NY
SU2C - OCRF - OCNA - NOCC Ovarian Cancer Dream Team Grant

- Mayo Clinic, Rochester, MN
- UW Medicine, Seattle, WA
- MD Anderson, Houston, TX
- UC Medicine, Chicago, IL
- NYU School of Medicine, New York, NY
- Dana-Farber Cancer Institute, Boston, MA
WISP enrollment to date

Distribution of Mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>27</td>
</tr>
<tr>
<td>BRCA2</td>
<td>8</td>
</tr>
<tr>
<td>RAD51C</td>
<td>1</td>
</tr>
<tr>
<td>PMS2</td>
<td>1</td>
</tr>
<tr>
<td>MSH6</td>
<td>2</td>
</tr>
<tr>
<td>MSH2</td>
<td>1</td>
</tr>
</tbody>
</table>
DNA Repair Dream Team

*Strengths of DNA Repair Dream Team*

- Diverse, complementary team of investigators from six world class institutions
- Novel therapeutic interventions for delivering near-term patient benefit
- Potential for reducing OC mortality through prevention
- Application of new basic science mechanisms to DNA repair profiling
- Biopsies from clinically-annotated PARPi trials
- Recent olaparib, rucaparib, niraparib approval
- Industry collaborations
- Committed advocates
Take home messages

- Defective DNA Repair in OvCA is a fundamental vulnerability of this cancer

- There is a lot of serendipity in science

- Need to support basic and clinical research simultaneously with a wide range of investigators

- Need to focus more on early detection, identification of women at risk, and prevention strategies
Thank You!

• GOAL: Eliminate death and suffering from ovarian cancer

• Requires everyone working together; patients and families, advocates, researchers, medical providers

• Support from Advocacy Community is essential
  • Raising awareness
  • Supporting research financially
  • Enrolling in clinical trials

SU2C-OCRFOCNA-NOCC Ovarian Cancer Dream Team Grant
DNA Repair Dream Team
Advocates

Jamie Crase  Kathleen Gavin  Deborah Polinsky
Panos Konstantinopoulos
William Barry
Alan D’Andrea

Ursula Matulonis
Geoffrey Shapiro
Giovanni Parmigiani
Alan D’Andrea, MD
Geoffrey Shapiro, MD, PhD
Ursula Matulonis, MD
Panagiotis Konstantinopoulos, MD, PhD
William Barry, PhD
Giovanni Parmigiani, PhD
Neal Horowitz, MD
Ariana Peralta
Karen Eldridge
Alexandra Feinstein
Don Watson

Gini Fleming, MD
Phillip Connell, MD
Olufunmilayo Olopade, MD
Anthony Montag, MD
Jane Churpek, MD
Iris Romero, MD
Morgan Whipkey, MD

Patient Advocates:
Jamie Crase, Kathleen Gavin, Deborah Polinsky

Elizabeth Swisher, MD
Mary-Claire King, PhD
Raymond Monnat, MD
Toshiyasu Taniguchi, MD, PhD
Deborah Bowen, PhD
Tomas Walsh, PhD
Barbara Norquist, MD
Maria Harrell, PhD
Steve Salipante, PhD
Kathy Agnew
Tara Coffin

Maria Jasin, PhD
Carol Aghajanian, MD
John Petretti, PhD
Elizabeth Kass, PhD
Kara Long Roche, MD
Jeanne Carter, PhD
Robert Soslow, MD
Rohit Prakash, PhD
Marcel Hohl, PhD

Scott Kaufmann, MD, PhD
John Weroha, MD, PhD
Larry Karnitz, PhD
Jamie Bakkum-Gamez, MD
Sarah E. Kerr, MD
Andrea Wahner Hendrickson, MD

Karen Lu, MD
Junjie Chen, PhD
Robert Coleman, MD
Denise Nebgen, MD, PhD
Anna Yemelyanova, MD
Mark Munsell, PhD
Santiago Ramirez-Vargas

Academic Collaborators:
Andre Nussenzweig, PhD (National Cancer Institute ), Douglas Levine, MD (NYU), Lewis Cantley, PhD (Weill Cornell Medical College), Martha Hickey, MD (University of Melbourne)